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REMARKS

Claims 20-33 are pending and under examination in the subject application. Applicants have hereinabove added new claims 34-41 and amended claims 20-23, 25, 28 and 31. Support for these amendments may be found, *inter alia*, in the subject specification as follows: claim 20: page 9, lines 3-13, and page 10, line 29 - page 11, line 2; page 10, line 29 - page 11, line 2; and page 13, lines 16-22; claim 21: page 11, lines 10-15; claim 22: page 11, lines 19-22; claims 23 and 28: page 12, lines 28-31; claim 25: page 13, lines 16-22; claim 31: page 11, lines 17-22 and page 13, lines 16-22; claim 34: page 10, line 29 - page 11, line 2; claim 35: page 10, line 29 - page 11, line 2; claim 36: page 10, line 29 - page 11, line 15, page 13, lines 3-8, and page 32, line 33 - page 33, line 9; claim 37: page 11, lines 24-35, and page 32, line 33 - page 33, line 9; claim 38: page 10, line 29 - page 11, line 2; claim 39: page 10, line 29 - page 11, line 2; claim 40: page 10, line 29 - page 11, line 15, page 13, lines 3-8, and page 32, line 33 - page 33, line 9; and claim 41: page 11, lines 24-35, and page 32, line 33 - page 33, line 9. Support for "head and neck squamous cell" in the claims may be found in the subject specification on page 8, lines 23-24, page 35, lines 24-25 and page 51, lines 18-19. Applicants maintain that these amendments raise no issue of new matter and respectfully request entry of this Amendment. Upon entry of this Amendment, claims 20-33 will still be pending and under examination.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the September 13, 2006 Office Action have been overcome and respectfully request that

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the Examiner reconsider and withdraw same.

Claim Rejections Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 20-29 and 31-33 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

In response, applicants respectfully traverse. Applicants appreciate the Examiner's suggestion but note that there is unclear support in the specification for "therapeutically effective amount." Thus, applicants have hereinabove amended claims 20, 25 and 31 to recite, in relevant part: wherein the amount of paclitaxel and C6-ceramide "is effective to induce a 50% death rate of" carcinoma cells or tumor cells as described on page 13, lines 19-22, of the subject specification. Applicants contend that these amendments obviate the above rejection. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

"in a subject"

The Examiner stated that claim 22 recites the limitation wherein the cell of claim 20 (e.g. leukemic cell, prostate cancer cell, pancreatic cancer cell, squamous carcinoma cell, breast carcinoma cell, myeloid leukemic cell or colon carcinoma cell) is present "in a subject." The Examiner alleged that claim 22 is indefinite because it is not clear that the subject being administered the agents of claim 20 is in need of such administration.

In addition, the Examiner stated that as claim 20 is drawn to

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a method of increasing apoptosis of a single cell, it is not clear how applicants intend to target administration to a single cell present in a subject.

In response, applicants respectfully traverse. Nevertheless, applicants have hereinabove amended claims 20 and 22. Claim 20, as amended, recites "tumor cells." Claim 22 has been amended to recite: "The method of claim 20, wherein the tumor cells are present in a subject." Applicants contend that these amendments obviate the above rejection. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

"CREMOPHOR"

The Examiner stated that claims 23 and 28 contain the trade name "CREMOPHOR." The Examiner notes that CREMOPHOR® is a registered trademark of BASF Pharma Solutions and does not comply with the requirements of 35 U.S.C. §112, second paragraph.

In response, applicants have hereinabove amended claims 23 and 28 to recite, in relevant part: "cremophore-mediated delivery." As described by applicants on page 12, lines 23-26 various cremophores are well known in the art such as oil based solvents. The term cremophore or any form of the term cremophore is used to describe a class of solvents, of which one member is marketed under the tradename CREMOPHOR®. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

In view of the above remarks, applicants maintain that the pending claims satisfy the requirement of 35 U.S.C. §112,

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second paragraph, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. §103(a)

Jayadev et al. in view of Mycek et al.

The Examiner maintained the rejection of claims 20, 25, 26 and 30-33 under 35 U.S.C. §103(a) as allegedly unpatentable over Jayadev et al. in view of Mycek et al.

The Examiner maintains that the combination of C6-ceramide and paclitaxel would have been *prima facie* obvious, as both agents were known in the art to be useful in the treatment of cancer. The Examiner stated that the skilled artisan, absent any testing, would have had a reasonable expectation that the two compounds would be effective in treating cancer when administered together.

(i) A *prima facie* case of obviousness does not exist

In response to the Examiner's rejection, applicants respectfully traverse and maintain that a *prima facie* case of obviousness does not exist with respect to any of the pending claims, and, in any event, would be rebutted by applicants' unexpected results.

There is no motivation to combine the cited references to create the invention set forth in claims 20, 25, 26 and 30-33. Jayadev et al. teach that C6-ceramide causes apoptosis in Molt-4 leukemia cells *in vitro*. Mycek et al. teach that a different agent, paclitaxel, can cause apoptosis in different types of cells, head and neck squamous cell carcinoma cells or

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metastatic breast cancer cells. Nowhere do Jayadev et al. teach or suggest that C₆-ceramide can cause apoptosis in head and neck squamous cell carcinoma cells or metastatic breast cancer cells; nowhere do Mycek et al. teach or suggest that paclitaxel can cause apoptosis in Molt-4 leukemia cells. These references teach treatment of different types of cancers by different agents. Since there is no known anti-cancer agent that can treat every type of cancer, there would have been no motivation for one of skill in the art to combine these references. Thus, the rejection is deficient at least in so far as it fails to show why one of skill in the art would have been motivated to combine such different teaching of these two references.

Furthermore, because the cited references teach treatment of different types of cancers by different agents, one of skill in the art could not have had a reasonable expectation that the combination would succeed. One of skill in the art is well aware that no known anticancer agent can treat every type of cancer. Thus, while hindsight reconstruction of the claimed invention may identify the cited references, one of skill in the art could not reasonably expect that the combination of C₆-ceramide and paclitaxel would work as set forth in claims 20, 25, 26 and 30-33.

Finally, Jayadev et al. in combination with Mycek et al. fail to teach each and every element set forth in new claims 34-37. New claims 34-37 recite prostate cancer, pancreatic cancer, myeloid leukemic and colon carcinoma and associated cells. Jayadev et al. and Mycek et al. when combined do not teach or suggest any of these types of cancers.

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Therefore, applicants maintain that Jayadev et al. in combination with Mycek et al. fail to motivate and fail to provide a reasonable expectation of success of the invention set forth in claims 20, 25, 26 and 30-37. Moreover, the combination of the references lack all of the elements of claims 34-37.

Accordingly, a *prima facie* case of obviousness has not been established against claims 20, 25, 26, 30-33 and new claims 34-37.

(ii) Applicants have unexpected results

Even if a *prima facie* case of obviousness could have been established, applicants' unexpected results rebut any such case. Specifically, the combination of paclitaxel and C6-ceramide induces apoptosis in a variety of cell lines in a more than additive amount as demonstrated in Table 2 on page 52 and discussed on page 54, lines 9-22 of this specification.

The art at the time the subject invention was made did not provide any guidance that a combination of C6-ceramide and paclitaxel would have any effect beyond that of each agent alone, let alone have a more than additive effect. Spencer et al., cited by the Examiner, showed the lack of predictability in the art. For example, Spencer et al. showed that: (i) the combination of paclitaxel and doxorubicin had a range of results from subadditive to synergistic depending upon the order of administration, cancer type, dose and timing of administration (page 806, column 2); and (ii) the combination of paclitaxel and vinblastine did not greatly alter the cytotoxicity of vinblastine alone (page 807, column 1).

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Applicants respectfully point out that the Examiner herself agrees that combination therapy is unpredictable as set forth in her argument on page 9 of the November 14, 2005 Office Action, wherein the Examiner cited column 1, lines 28-37, of U.S. Patent No. 6,664,288 for the following teaching:

"Combination therapies, while desirable, are a hit or miss proposition. The treatments are typically not additive. In many cases, cross effects and treatment load can result in lower effectiveness for the combinations, than either treatment alone."

Therefore, applicants' results in Table 2 on page 52 are unexpected. Such unexpected results rebut a *prima facie* case of obviousness even if there was one.

In view of the above remarks, applicants maintain that claims 20, 25, 26, 30-33 and new claims 34-37 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the Examiner reconsider and withdraw the rejection based on Jayadev et al. in view of Mycek et al.

Spencer et al. in view of Cai et al.

The Examiner maintained the rejection of claims 20-33 under 35 U.S.C. §103(a) as allegedly unpatentable over Spencer et al. in view of Cai et al.

(i) Applicants have unexpected results

In response to the Examiner's rejection, applicants respectfully traverse and maintain that even if a *prima facie*

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case of obviousness could be established against any of the pending claims, applicants' unexpected results rebut any such case.

As discussed above, the combination of paclitaxel and C6-ceramide induces apoptosis in a variety of cell lines in a more than additive amount as demonstrated in Table 2 on page 52 and discussed on page 54, lines 9-22 of this specification.

The art at the time the subject invention was made did not provide any guidance that a combination of C6-ceramide and paclitaxel would have any effect beyond that of each agent alone, let alone have a more than additive effect. Spencer et al., cited by the Examiner, showed the lack of predictability in the art. For example, Spencer et al. showed that: (i) the combination of paclitaxel and doxorubicin had a range of results from subadditive to synergistic depending upon the order of administration, cancer type, dose and timing of administration (page 806, column 2); and (ii) the combination of paclitaxel and vinblastine did not greatly alter the cytotoxicity of vinblastine alone (page 807, column 1).

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"Combination therapies, while desirable, are a hit or miss proposition. The treatments are typically not additive. In many cases, cross effects and treatment load can result in lower effectiveness for

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the combinations, than either treatment alone."

Therefore, applicants' results in Table 2 on page 52 are unexpected. Such unexpected results rebut a *prima facie* case of obviousness even if there was one.

(ii) A *prima facie* case of obviousness does not exist

In any event, a *prima facie* case of obviousness does not exist with respect to new claims 38-41.

There is no motivation to combine the cited references to create the invention set forth in claims 38-41. Spencer et al. teach that paclitaxel causes inhibition or death of cancer cells in leukemia, prostate cancer, pancreatic cancer, head and neck squamous carcinoma, breast carcinoma, colon carcinoma and myeloid leukemia. Cai et al. teach that a different agent, C6-ceramide, can cause apoptosis in a breast carcinoma cell line. Nowhere do Cai et al. teach or suggest that C6-ceramide can cause apoptosis in the cancer cells of leukemia, prostate cancer, pancreatic cancer, head and neck squamous carcinoma, colon carcinoma and myeloid leukemia. These references teach treatment of different types of cancers with different agents. Since there is no known anti-cancer agent that can treat every type of cancer, there would have been no motivation for one of skill in the art to combine these references. Thus, the rejection is deficient at least in so far as it fails to show why one of skill in the art would have been motivated to combine such different teachings of these two references.

Furthermore, because the cited references teach treatment of different types of cancers by different agents, one of skill

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in the art could not have had a reasonable expectation that the combination would succeed. One of skill in the art is well aware that no known anticancer agent can treat every type of cancer. Thus, while hindsight reconstruction of the claimed invention may identify the cited references, one of skill in the art could not reasonably expect that the combination of C₆-ceramide and paclitaxel would work as set forth in claims 38-41.

Therefore, applicants maintain that Spencer et al. in combination with Cai et al. fail to motivate and fail to provide a reasonable expectation of success of the invention set forth in claims 38-41.

Accordingly, a *prima facie* case of obviousness has not been established against claims 38-41.

In view of the above, applicants maintain that claims 20-33 and new claims 38-41 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the Examiner reconsider and withdraw the rejection based on Spencer et al. in view of Cai et al.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and earnestly solicit allowance of claims 20-41.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants'

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undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed \$510.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

 3/13/07
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Date